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(19)

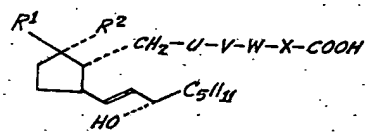
(54) PROSTENOIC ACIDS AND PROCESS FOR THEIR MANUFACTURE

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt (Main) 80, Postfach 80 03 20, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to analogues of prostenoic acids and a process for their manufacture.

Prostaglandins are a group of natural substances which have been isolated from different animal tissues. In mammals they are responsible for a great number of physiological actions. The natural prostaglandins have a carbon skeleton containing, in general, 20 carbon atoms and are distinguished, above all, by a major or minor content of hydroxyl groups or double bonds in the cyclopentane ring; (the structure and action of prostaglandins are described, i.a. in M. F. Cuthbert "The Prostaglandins, Pharmacological and Therapeutic Advances", William Heinemann Medical Books Ltd., London (1973)).

The present invention provides analogues of prostenoic acids of the general formula I

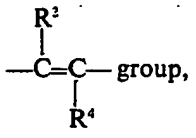


(I)

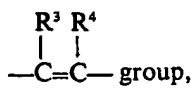
wherein

R^1 and R^2 together represent an oxygen atom or one represents a hydrogen atom and the other represents a hydroxyl group;

U represents a $(CH_2)_m$-group, m being 0 or an integer of from 1 to 5, an

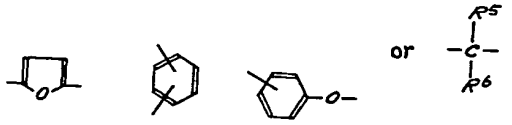


wherein R^3 and R^4, which may be identical or different, each represents a hydrogen atom or an alkyl group having up to 5 carbon atoms, or an



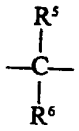
wherein R^3 and R^4 are as defined above;

V represents a direct bond, an oxygen atom or a radical of the formula



wherein R^5 and R^6, which may be identical or different, each represents a hydrogen atom or an alkyl group having up to 5 carbon atoms,

W represents a direct bond or a radical of the formula



wherein R^5 and R^6, which may be identical or different, each represents a hydrogen atom or an alkyl group having up to 5 carbon atoms;

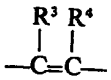
X represents a $(CH_2)_m$-group, where m is 0 or an integer of from 1 to 5; subject to the following provisos:

(i) when U represents a $(CH_2)_m$ group, V, W and X together do not represent a straight-chain alkylene group, an alkylene group in which the carbon atom adjacent to the carboxyl group (position 2) is substituted by one alkyl group, or an alkylene group in which the carbon atom in position 3 is substituted by two alkyl groups,

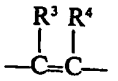
(ii) when U represents a $(CH_2)_m$ group and V and W both represent direct bonds, X does not represent a $(CH_2)_m$ group in which m is 0,

(iii) when U represents a $(CH_2)_m$ group and V represents an oxygen atom, W and X together do not represent a methylene group, or a trimethylene group which may be substituted by one alkyl group, and

(iv) when U represents the group



in which R^3 and R^4 both represent hydrogen atoms, V, W and X together do not represent an alkylene group having up to 10 carbon atoms with 1 to 5 carbon atoms in the chain between the carboxyl group and the



group.

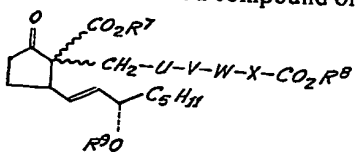
The invention further provides the salts of these compounds with inorganic or organic bases, especially the physiologically tolerable salts.

These prostanoic acid analogues do not occur naturally.

U preferably represents a polymethylene chain having up to 3 methylene groups. Of the other radicals mentioned for U those in which R^3 or R^4 each represents an alkyl radical having up to 3 carbon atoms are preferred. The members V, W and X preferably together form a branched alkylene radical having up to 10 carbon atoms, an oxa-branched alkylene radical having up to 9 carbon atoms, or an oxa-straight chain alkylene radical having up to 6 carbon atoms. If V represents a phenylene or phenoxy radical, the group —W—X—COOH may be in the *o*-, *m*- or *p*-position.

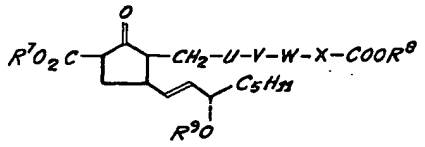
The invention further provides a process for the manufacture of a compound of the general formula I, which comprises

a) reacting an alkali metal alkoxide with a compound of the general formula II



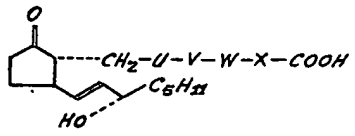
(II)

wherein U, V, W and X are defined as above and
R^7 represents an alkyl group having up to 5 carbon atoms,
R^8 represents an alkyl group having up to 5 carbon atoms,
R^9 represents an unsubstituted or substituted alkyl group having up to 20 carbon atoms, an aryl radical or a cycloalkyl radical having from 5 to 8 carbon atoms wherein a CH_2-group may be replaced by an oxygen atom, and subjecting the reaction product of the general formula III



(III)

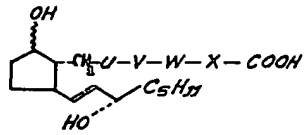
wherein the radicals R^7, R^8 and R^9 and U, V, W and X are defined as in the formula II, to alkaline hydrolysis, decarboxylation and removal of the protective group from the 15-position in the presence of an acid catalyst, after which reactions a compound of the general formula Ia



(Ia)

wherein U, V, W and X are defined as above, or a salt thereof with an inorganic and organic bases is obtained; and, if desired,

b) reducing a compound of the general formula Ia with a complex metal hydride to give a compound of the general formula Ib



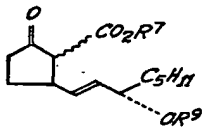
(Ib)

wherein the 9-hydroxy group may be in the α- or β-configuration, and U, V, W and X are defined as above, and, if desired,

c) converting a resulting salt into the free acids or a resulting salt into the free acid or another salt.

Starting compounds of the formula II are described and claimed, for example, in our co-pending Application No. 27142/74 Serial No. 1,466,298 and may be obtained according to the methods described therein.

This process comprises reacting, for example a compound of the formula IIa



IIa

wherein R^7 and R^9 are defined as in the formula II, in an aprotic solvent in the presence of a base with a halogen carboxylic acid ester of the formula IIb

$$Hal—CH_2—U—V—W—X—CO_2R^8 \qquad \text{IIb}$$

wherein U, V, W, X and R^8 are defined as in the formula II. The reaction is advantageously carried out at a temperature ranging from room temperature to 140°C under an inert atmosphere. Suitable aprotic solvents are benzene, toluene or xylene. As the base, there is preferably used anhydrous sodium ethoxide or potassium tertiary butoxide.

The compounds of the formula IIa can be obtained according to the Belgian Patent Specification No. 766,521.

Step (a) of the process is a retro-Dieckmann-condensation, and is preferably carried out in the presence of from 1 to 1.5 moles of an alkali metal alkoxide in an alcohol (cf. Belgian Patent Specification No. 766,521) at a temperature from room temperature to 150°C for 1 to 16 hours under an atmosphere of an inert gas. The reaction product of the general formula III is subjected, generally after the usual working up procedure and sometimes after further purification by chromatography to alkaline hydrolysis, decarboxylation, and then removal of the protective group from the 15-position in the presence of an acid catalyst (cf. also Belgian Patent Specification No. 766,521).

A compound of the formula III is preferably prepared as follows:

A compound of the general formula II (obtainable according to our co-pending Application No. 27142/74 Serial No. 1,466,298) is dissolved in an anhydrous solution of 1 to 1.5 moles of an alkali metal alkoxide in an alcohol, preferably sodium ethoxide in ethyl alcohol, and this solution is stirred with the exclusion of oxygen and moisture for 1 and 16 hours at a temperature of from 20 to 150°C. The reaction time and the reaction temperature depend on the reactivity of the compound of formula II used. Generally the reaction is carried out at a temperature of from 50 to 90°C for 2 to 6 hours. The reaction may be stopped by heating in benzene or a xylene solution to a temperature of up to 150°C. Acidification is then carried out under careful conditions, advantageously using an acidic salt of a poly-basic acid and then the product is worked up in usual manner. The resulting compound of the general formula III may be purified by chromatography on silica gel.

It is, however, advantageous to use the following procedure: the crude compound of the general formula III is hydrolysed directly with an alcoholic-aqueous solution of a base. The resulting solution is then acidified with a dilute acid, and the resulting dicarboxylic acid is isolated from the aqueous solution by extraction with an organic liquid. The dicarboxylic acid is then decarboxylated by heating for 1 to 4 hours at 80° to 110°C. in benzene or toluene in the manner usual for β-ketoacids. R^9, the protective group of the alcohol function in the 15-position is then preferably split off by hydrolysis with an aqueous solution of an organic acid, for example, 70% aqueous acetic acid or 2% aqueous-alcoholic oxalic acid.

The resulting crude compound of the general formula Ia may be purified by chromatography, for example, by applying a solution of the compound in a cyclohexane/ethyl acetate mixture to a column of silica gel and eluting the compound using the same cyclohexane/ethyl acetate mixture to which acetic acid has been added. Such compounds are racemates and can be used as such. However, it is also possible to separate a compound of the general formula Ia into its optical antipodes by the formation of salt with an optically active base.

A compound of the formula Ia is reduced to a compound of the formula Ib according to method b) by means of a complex metal hydride, advantageously with a metal borohydride, for example, zinc borohydride in an organic solvent, or an alkali metal borohydride, for example, sodium borohydride in an aqueous-organic medium or in an alcoholic solution.

The reaction produce of formula Ib may be worked up in usual manner and purified by chromatography. The compounds obtained thus are epimers with respect to the 9-position, and may be used directly or may be separated according to one of the usual separation methods for stereo-isomers, for example, with the aid of thin-layer-chromatography. When a racemic compound of the general formula Ia is used as the starting material, a racemic compound (with respect to the 8 and 12-position) of the general formula Ib is obtained. The antipodes may be separated after the formation of salt with an optical base.

A free acid of formula I may be converted into a salt, preferably a physiologically tolerable salt, according to methods known *per se*. Suitable salts are, for example, alkali metal salts and triethanolammonium or benzylammonium salts.

Compounds of the general formula I are optionally racemic prostenoic acids. (The nomenclature can be referred to *inter alia* in N. Andersen, Annals of the New York Academy of Sciences, Volume 180, Prostaglandins, page 14).

In addition to those compounds named in the Examples, the following compounds are preferred:

List A

9ξ,15α-dihydroxy-6-methyl-3-oxa-5-*cis*-13-*trans*-prostadienoic acid
9ξ,15α-dihydroxy-5-methyl-3-oxa-5-*trans*-13-*trans*-prostadienoic acid
6,6-diethyl-15α-hydroxy-9-oxo-13-*trans*-prostenoic acid
9ξ,15α-dihydroxy-4,4-dimethyl-13-*trans*-prostenoic acid
9ξ,15α-dihydroxy-2,2-dimethyl-3-oxa-13-*trans*-prostenoic acid.

The compounds of the general formula I are distinguished as compared with their closely related natural products by differentiated pharmacological effects. The compounds of the general formula Ia excel, for example by a marked spasmogenic activity.

For example, when a CH_3-group is introudced into hydroxy-9-oxo-13-*trans*-prostenoic acid in the 2-, 3-, 4- or 5-positions (Examples 4, 5, 6 and 7), the spasmogenic activity is least in the 2-methyl compound, but increases progressively in the 3-, 4- and 5-methyl compounds.

15α-Hydroxy-5-methyl-9-oxo-13-*trans*-prostenoic acid (Example 4) shows good spasmogenic activity, a blood-pressure lowering activity which is reduced compared with 15α-hydroxy-9-oxo-13-*trans*-prostenoic acid, and a good bronchodilating activity.

The pharmacological activity was determined in the following tests:

Effect on smooth muscle (isolated rat stomach according to Vane, Br. J. Pharmac. Chemother., 12 344 (1957))

The test was carried out on Wistar rats of both sexes having a weight of 200 to 220 g. The animals were killed by a blow on the neck, the stomach was rapidly removed and put into a Petri dish containing a pre-heated Krebs solution. The fundus, which is easily distinguished from the pyloric part because of its grey color, was separated and opened longitudinally. From this was cut a transverse strip which was suspended in an organ bath which contained the usual Krebs solution, which was maintained at a temperature of 37°C and through which was bubbled a mixture of 95% O_2 and 5% CO_2. A writing lever charged with 1 g served to register on a kymograph the contractions produced by adding the substance to be examined to the bath. The test criterion was the contraction occurring after the addition of the substance to be examined. The degree of activity was determined by comparing the contraction occurring after the addition of 600 ng/ml PGA_2. The values expressed in % with regard to the comparison preparation were used to draw a dose-activity-curve which enabled the medium activity dose to be determined.

All substances were present as stock-solutions in absolute alcohol and were diluted to their final concentration with phosphate buffer (pH = 7.4).

Test of intravenously administered preparations for bronchospasmolytic activity according to Konzett-Rössler

Except for irrelevant modifications, the test arrangement used largely corresponded to the description given by H. Konzett and R. Rössler, Arch. exp. Path. Pharmakol. *195*, 71 (1940)). Test animals were male white Guinea pigs having a weight of 400 to 500 g. They were anesthesized with hexobarbital and urethane. All preparations to be administered were diluted with phosphate buffer (pH = 7.4) and administered in a volume of 0.1 ml.

In the test arrangement, the test animal is compelled to breathe air which is maintained at above atmospheric pressure by a pump in connection with a relief valve. By this means the air volume in the respiratory tract is kept constant. Modifications in the capacity of the respiratory tract caused by the tested compounds can be determined as an increase or decrease of the air volume absorbed by the lung under the given constant blowing pressure. To produce a heavy bronchospasm acetylcholine or histamine were injected by the intravenous route. The dosage unit of the irritant was chosen such that an about 70 to 80% decrease of the absorption capacity of the lung was obtained. The substance to be examined was administered by the intravenous route in the *V. jugularis*. 30 seconds thereafter the already evaluated dosage unit of the irritant was injected. The medium inhibition dose was read off from the dose activity curve drawn either graphically or by means of regression analysis.

Test for the effect on the blood circulation

The hyp tensive properties were examined in accordance with the methods described by Kannegiesser and Lee, Nature *229*, 498 (1971).

Test animals were cats of both sexes having a weight of 2.0 to 3.0 kg.

The animals were anesthesized with pentobarbital in an amount of 1.7 to 2.8 mg/ml in 0.9% NaCl-solution as continuous infusion with 5 mg/kg/hour and pretreated with pentolinium (Ansolysen, May & Baker) with 10 mg/animal by the intraperitoneal route. The test substances were administered through the *Vena jugularis*. The blood pressure was measured in the *A. carotis ext.* directly and recorded by means of a Statham pressure sensor on a multi-channel recorder.

The maximum change of the systolic and diastolic blood pressure was measured in mm Hg.

All test preparations were present as stock solutions in absolute alcohol and were diluted to the end concentration immediately before the test with phosphate buffer (pH = 7.4).

Compounds that show good bronchodilatory properties with diminished blood pressure action are of great importance for medicinal use, for example, against an acute asthma attack.

The following Table 1 shows the spasmogen, blood-pressure lowering and bronchodilatory properties of certain compounds coming within the scope of this invention.

Example	Action on smooth muscle (isolated rat stomach) ED_{50} (μg/ml)	Bronchospasmolysis ID_{50} (μg/kg i.v.) Histamine acetylcholine (Guinea pig)		Blood pressure (modifications in mm Hg) after 5 μ/kg i.v. (cat)
6 rac. 15α-Hydroxy-3-methyl-9-oxo-13-*trans*-prostenoic acid	1.0	4.0	1.0	-10/-20
5 rac. 15α-Hydroxy-4-methyl-9-oxo-13-*trans* prostenoic acid	0.5	0.9	0.5	-45/-50
4 rac. 15α-Hydroxy-5-methyl-9-oxo-13-*trans* -prostenoic acid	0.2	0.02	0.4	-20/-30

The compounds of the general formula Ib have a good spasmogenic action, for example the ED_{50} in the isolated rat stomach for rac. 9ξ,15α-dihydroxy-3-oxa-5-*trans*-13-*trans*-prostadienoic acid (Example 25 A) is 3.1 μg/ml.

A further advantage of the compounds of the invention is their comparatively higher stability towards acids and bases than prostaglandins of the E and F series.

The compounds of the present invention therefor are differentiated in their pharmacological properties compared with their naturally occurring analogues and are superior to the natural prostaglandins in the treatment of certain diseases, for example, bronchial asthma, high blood pressure, and oedemas.

Accordingly, the inventions further provides a pharmaceutical preparation which comprises a compound of the general formula I or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier.

The preparations of the invention may comprise the compounds of the invention in the form of aqueous solutions or suspensions, or as solutions in other pharmaceutically suitable organic solvents, for example mono- or polyvalent alcohols, dimethylsulfoxide or dimethylformamide or N,N-dimethylacetamide. The pharmaceutically suitable carrier may be a polymer carrier, for example, polyvinyl pyrrolidone. The preparations may be in a form suitable for administration by infusion or injection, or orally, rectally or topically, for example, tablets, ointments, emulsions, suppositories and aerosoles.

For the oral forms, the active compounds is preferably mixed with carriers known *per se* and brought into suitable dosage unit forms by methods known *per se*, for example, tablets, dragees or gelatin capsules. As inert carriers, for example, magnesium carbonate, lactose or corn starch with the addition of other substances, for example, magnesium stearate can be used, and the preparation may be manufactured *via* dry or moist granules.

The preparations are preferably in unit dosage form, and one dosage unit contains preferably from 1 mg to 10 mg of a compound of the invention. A suitable daily dosage is from 10 to 100 mg of a compound of the invention.

The preparations may comprise compounds together with one or more other pharmacologically active substances, for example, diuretic, hypotensive, and anti-asthmatic agents.

The following Examples illustrate the invention. In the examples, 'ether' is diethyl ether and the ratios of eluants in eluant mixtures are calculated by volume.

EXAMPLE 1.

rac. 15α-Hydroxy-9-oxo-1,5-inter-*p*-phenylene-2,3,4-trinor-13-trans-prostenoic acid

a. rac. ethyl 10-ethoxycarbonyl-9-oxo-15α-tetrahydropyran-2'-yloxy-1,5-inter-p-phenylene-2,3,4-trinor-13-trans-prostenoate

1.6 g (3.5 mmoles) of ethyl (5*RS*, 3''' *SR*)-1-[3'-(4''-ethoxycarbonylphenyl)-propyl] - 2 - oxo - 5 - [3'''-(2''''-tetrahydropyranyloxy)-*trans*-1'''-octenyl] - cyclo - pentanecarboxylate and 4.15 ml of an anhydrous solution of sodium ethoxide in ethanol were heated to boiling for 6 hours (85—90° bath temperature). The analysis of the reaction mixture by thin-layer chromatography showed that all of the starting material had been consumed (Al_2O_3-plates and cyclohexane/ether 1:1 were used as eluent). After the addition of 20 ml of dry toluene the ethanol was evaporated off and the resulting solution was cooled to −10°C. 4.5 ml of aqueous 2 N NaH_2PO_4-solution were added to the cooled solution while stirring. The organic phase was again washed with water and dried over $MgSO_4$. After evaporation 1.53 g of crude product were obtained which was chromatographed on 120 g of silica gel (Merck, 70—230 mesh ASTM).

Eluant: 200 ml cyclohexane/ethyl acetate/triethylamine 90:10:1
900 ml cyclohexane/ethyl acetate/triethylamine 80:20:1

Fractions of 8 ml were taken off. From fractions 52 to 130 870 mg of oily product were obtained.

Rf = 0.57 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1)

NMR: 7.65 ppm (4H, quadruplet); 5.5 ppm (2H) 4.65 ppm (1H) 4.5 to 3.4 ppm

b. rac. 15α-Hydroxy-9-oxo-1,5-*inter*-*p*-phenylene-2,3,4-trinor-13-trans-prostenoic acid

710 mg (1.3 mmoles) of rac. ethyl 10-ethoxycarbonyl-9-oxo-15α-tetrahydro-

pyran-2'-yloxy-1,5-*inter-p*-phenylene-2,3,4-trinor-13-*trans*-prostenoate were heated in 20 ml methanol and 14 ml 0.6 N sodium hydroxide solution for 6 hours while stirring to 60—65°C. The methanol was evaporated off on a rotary evaporator under reduced pressure and the remaining aqueous solution was washed twice with ether and then saturated with NaCl. The product was triturated with ether and the resulting solution was acidified with hydrochloric acid while cooling and stirring to pH 1 to 2. The aqueous phase was again extracted three times with ether, the combined organic phases were washed once with water and dried over anhydrous Na_2SO_4. After evaporating off the ether, 620 mg of oily material were obtained which were heated with 7 ml of ethanol and 5 ml of 2% aqueous oxalic acid for 1 hour to 60—65°C. After evaporating off the ethanol under reduced pressure the material was distributed between ether and water, and, after drying over $MgSO_4$, the organic phase was evaporated. The oily residue was chromatographed on 40 g of silica gel (Merck, 70—230 mesh ASTM) with cyclohexane/ethyl acetate/glacial acetic acid 60:40:1, fractions of 4 ml being collected. Fractions 57 to 76 yielded 260 mg of crystalline product after evaporation. m.p.: 110—113°C.

Rf = 0.29 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1)

NMR: 7.65 ppm (4H, quadruplet), 6.85 ppm (2H, 5.6 ppm (2H) 4.1 ppm (1H).

EXAMPLE 2.

rac. 15α-Hydroxy-3-methyl-9-oxo-4,5,6-trinor-13-*trans*-prostenoic acid

a. rac. ethyl 10-ethoxycarbonyl-3-methyl-9-oxo-15α-tetrahydropyranyloxy-4,5,6-trinor-13-*trans*-prostenoate

2.5 g (5 mmoles) of ethyl (5*RS*,3''*SR*)-1-(3'-ethoxycarbonyl-2'-methylpropyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate were heated in 5.8 ml of 0.93 N sodium ethoxide solution in absolute ethanol (5.4 mmoles) for 6 hours to 80°C and after the addition of 25 ml absolute toluene the solvent was distilled off up at temperatures to the boiling point of 110°C (normal pressure). The solution was cooled to 0°C, 10 ml of 25% sodium dihydrogenphosphate solution and 20 ml of ice-cold, saturated sodium chloride solution were added, and the solution was shaken four times with 100 ml of diethyl ether. The combined ether extracts were washed three times with 20 ml of H_2O, dried over Na_2SO_4, and the solvent was distilled off under reduced pressure. The residue was chromatographed on silica gel (Merck, height of the column filling 22 cm, diameter 3.2 cm) and eluted with the following solvent mixtures dividing it into 310 fractions:

Solvent		Fractions	
750 ml	cyclohexane/ethyl acetate/	1—75	16 mg
	triethyl amine	76—130	60 mg
	95:5:1	131—159	184 mg
750 ml	cyclohexane/ethyl acetate/	160—310	1264 mg
	triethyl amine		
	90:10:1		
300 ml	ethyl acetate	—	584 mg
300 ml	methanol	—	354 mg

The fractions 131 to 159 contained 184 mg of slightly contaminated rac. ethyl 10-ethoxycarbonyl-3-methyl-9-oxa-15α-tetrahydropyran-2'-yloxy-4,5,6-trinor-13-*trans*-prostenoate and the fractions 160 to 310 1264 mg of pure product.

b. rac. 3-Methyl-9-oxo-15α-tetrahydropyran-2'-yloxy-4,5,6-trinor-13-trans-prostenoic acid

1.26 g of the above ester were stirred in 20 ml of methanol with 5.1 ml of 1 N NaOH for 48 hours at room temperature and for 5 hours at 50°C under argon, the solvent was distilled off und r reduced pressure, 20 ml of saturated NaCl-solution, were added to the residue, the resulting mixture was acidified with 2 N HCl to pH

l and then extracted three times with 150 ml of ether. The combined ether extracts were washed until the washings were neutral, dried over Na_2SO_4, concentrated to 1.18 g of yellow oil, which was h ated under reflux in 50 ml of benzene for 1 hour and the solvent was evaporated off under reduced pressure.

c. rac. 15α-Hydroxy-3-methyl-9-oxo-4,5,6-trinor-13-*trans*-prostenoic acid

The residue obtained in Example 2b was heated with 18 ml of 2% oxalic acid solution in 30 ml of methanol for 2 hours at 50°C, and then the methanol was distilled off under reduced pressure. The aqueous residue was extracted three times with 150 ml of diethyl ether, the combined ether extracts were washed twice with 20 ml of water, dried over sodium sulfate, and concentrated under reduced pressure. 1.023 g of residue were obtained. The brownish oil was chromatographed on silica gel (Merck, height of the column filling 18 cm, diameter 2.2 cm).

Solvent		Fractions	
750 ml	cyclohexane/ethyl acetate/	1 to 160	56 mg
	glacial acetic acid	161 to 220	60 mg
	66:33:1	221 to 245	320 mg
		246 to 255	134 mg
500 ml	of cyclohexane/ethyl	256 to 350	303 mg
	acetate/glacial acetic acid		
	59:40:1		
300 ml	methanol		42 mg

The fractions 246 to 255 contained 135 mg of slightly contaminated rac. 15α-hydroxy-3-methyl-9-oxo-4,5,6-trinor-13-*trans*-prostenoic acid, and the fractions 256 to 350 contained 303 mg of this product.

Rf on silica gel plates (Merck, cyclohexane/ethyl acetate/glacial acetic acid 60:40:1) = 0.1

NMR in $CDCl_3$ singulet 7.55 ppm (2H)

multiplet 5.4—5.6 ppm (2H)

multiplet 4—4.15 ppm (1H)

EXAMPLE 3.

rac. 15α-Hydroxy-3-oxa-9-oxo-5-trans-13-trans-prostadienoic acid

1.76 g (3.5 mmoles) of ethyl (5*RS*,3''*SR*)-1-(6'-methoxycarbonyl-5'-oxa-*trans*-2'-hexenyl) - 2 - oxo - 5 - [3'' - (2''' - tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate were heated under argon with 3.6 ml (3.6 mmoles) of freshly prepared sodium ethoxide solution for 3½ hours at 80°C. To the solution, cooled to 0°C, 20 ml of ice-cold NaH_2PO_4-solution were added, the solution was shaken with 500 ml of diethyl ether, washed with water, dried and concentrated. 1.8 g of light coloured oil were obtained, which was dissolved in 16 ml of methanol and stirred with 16 ml of 0.6 NaOH for 3.5 hours at room temperature. The solution was concentrated under reduced pressure, acidified with 2N HCl to pH 2, extracted with 2 x 200 ml of diethyl ether, washed with water, dried and concentrated. 1.6 g of a yellow oil that had formed was boiled under reflux in 30 ml of benzene for 1 hour. The benzene was distilled off under reduced pressure and the residue was dissolved in 25 ml of ethanol and stirred with 25 ml of 2% oxalic acid solution for 6 hours at room temperature. The ethanol was distilled off under reduced pressure, the aqueous solution was extracted with 2 x 200 ml of diethyl ether, and the ether phase was washed, dried and concentrated. 1.53 g of crude product that were chromatographed on 50 g of silica gel (Merck).

Solvent	Fraction	
300 ml of cyclohexane/ethyl acetate/ glacial acetic acid 80:20:1		
300 ml of cyclohexane/ethyl acetate/ glacial acetic acid 70:30:1	1—240	157 mg
300 ml cyclohexane/ethyl acetate/ glacial acetic acid 60:40:1		
350 ml of cyclohexane/ethyl acetate/ glacial acetic acid 60:40:1	241—400	690 mg
350 ml of cyclohexane/ethyl acetate/ glacial acetic acid 50:50:1		
350 ml of cyclohexane/ethyl acetate/ glacial acetic acid 50:50:1	401—550	143 mg
400 ml of methanol		336 mg

Substance in pure state (fractions 241—400): 690 mg
Rf = 0.18 (silica gel, cyclohexane/ethyl acetate 70:35)
NMR ($CDCl_3$) 6.1 ppm (2H, singulet)
5.5—5.7 ppm (2H, multiplet)
3.9—4.4 ppm (5H, singulet and multiplet)

EXAMPLE 4.

rac. 15α-Hydroxy-5-methyl-9-oxo-13-trans-prostenoic acid

This compound was obtained in a manner analogous to that described in Example 3, from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-3'-methylhexyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.
Rf = 0.33 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1)
NMR: 7.6 ppm (2H), 5.55 ppm (2H), 4.2 ppm (1H)

EXAMPLE 5.

rac. 15α-Hydroxy-4-methyl-9-oxo-13-trans-prostenoic acid

This compound was prepared in an analogous manner to that described in Example 3, starting from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbnoyl-4'-methylhexyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl - cyclopentanecarboxylate
Rf = 0.31 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1)
NMR: 7.2 ppm (2H), 5.6 ppm (2H), 4.2 ppm (1H)

EXAMPLE 6.

rac. 15α-Hydroxy-3-methyl-9-oxo-13-trans-prostenoic acid

The compound was prepared by a process analogous to that described in Example 3, starting from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-5'-methylhexyl)-2 - oxo - 5 - [3'' - (2''' - tetrahydropyranyloxy) - *trans* - 1'' - octenyl] - cyclopentanecarboxylate.
Rf = 0.34 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1)
NMR: 6.4 ppm (2H), 5.6 ppm, (2H), 4.15 ppm (1H).

EXAMPLE 7.

rac. 15α-Hydroxy-3-methyl-4-oxa-9-oxo-13-*trans*-prostenoic acid

Reactions were effected analogously to those described in Example 3 but starting from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-5'-methyl-4'-oxahexyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.
Rf = 0.1 (silica gel, cyclohexane/ethyl acetate/glacial acetic acid 30:70:1)
NMR: 6 to 6.1 (2H, singulet), 5.5 to 5.7 ppm (2H, multiplet), 3.6 to 4.4 ppm (4H, broad signal).

EXAMPLE 8.

rac. 15α-Hydroxy-3-oxa-9-oxo-5-*cis*, 13-*trans*-prostadienoic acid

This compound was prepared by a method analogous to that described in Example 3, starting from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-5'-oxa-*cis*-2'-hexenyl)-2-oxo-5-[3''-(2''' - tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.

Rf = 0.5 (ethyl acetate, methanol 70:35, silica gel)

NMR: 6.85 ppm (2H, singulet)
5.7—5.9 ppm (4H, multiplet)
4—4.3 ppm (5H, singulet and multiplet)

EXAMPLE 9.

rac. 15α-Hydroxy-2-methyl-3-oxa-9-oxo-13-trans-prostenoic acid

Reactions analogous to those described in Example 3 were carried out, starting from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-5'-oxaheptyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.

Rf = 0.13 (silica gel, cyclohexane/ethyl acetate/glacial acetic acid 30:70:1

NMR: 6.4 ppm (2H, singulet)
5.5—5.7 ppm (2H, multiplet)
3.4—4.2 ppm (4H, broad signal)

EXAMPLE 10.

rac. 15α-Hydroxy-3-oxa-9-oxo-2a-homo-5-*cis*, 13-*trans*-prostadienoic acid

This compound was prepared by a process carried out in an analogous manner to that described in Example 3, starting from ethyl (5*RS*,3''*SR*)-1-(7'-methoxycarbonyl-5'-oxa-*cis*-2'-heptenyl)-2-oxo-5-[3'' - (2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.

Rf = 0.15 (silica gel, cyclohexane/ethyl acetate/glacial acetic acid 60:40:1)

NMR: 6.95 ppm (2H, singulet)
5.4—5.7 ppm (4H, multiplet)
3.9—4.4 ppm (5H, multiplet)

EXAMPLE 11.

rac. 15α-Hydroxy-9-oxo-4,7-*inter*-o-phenylene-5,6-dinor-13-trans-prostenoic acid

The above compound was prepared in a manner analogous to that described in Example 3, starting from ethyl (5*RS*,3''*SR*)-1-[2'-(3''-ethoxycarbonylpropyl)-benzyl] - 2 - oxo - 5 - [3''' - (2'''' - tetrahydropyranyloxy) - *trans*-1'''-octenyl]-cyclopentanecarboxylate.

Rf = 0.26 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1)

NMR: 7.1 ppm (4H), 6.7 ppm (2H), 5.45 ppm (2H).

EXAMPLE 12.

rac. 15α-Hydroxy-9-oxo-3,7-*inter-p*-phenylene-4,5,6-trinor-13-trans-prostenoic acid

This compound was prepared analogously to that described in Example 3, starting from ethyl (5*RS*,3''*SR*)-1-[4'-(2''-ethoxycarbonylethyl)-benzyl]-2-oxo-5-[3'''-(2''''-tetrahydropyranyloxy)-*trans*-1'''-octenyl]-cyclopentanecarboxylate.

Rf = 0.30 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1)

NMR: 7.1 ppm (4H), 6.8 ppm (2H), 5.5 ppm (2H), 4.05 ppm (1H).

EXAMPLE 13.

rac. 15α-Hydroxy-9-oxo-1,7-*inter-p*-phenylene-2,3,4,5,6-pentanor-13-trans-prostenoic acid

The reactions carried out were analogous to those described in Example 3, starting from ethyl (5*RS*,3''*SR*)-1-(4'-ethoxycarbonylbenzyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.

Melting point: 106 to 107°C.

Rf = 0.30 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1)

NMR: 7.65 ppm (4H, quadruplet), 6.7 ppm (2H), 5.55 ppm (2H), 4.05 ppm (1H), 2.97 ppm (2H).

EXAMPLE 14.

rac. 15α-Hydroxy-5-oxa-9-oxo-1,5-*inter-p*-phenylene-2,3,4-trinor-13-trans-prostenoic acid

This compound was prepared by a process analogous to that described in

Example 3, starting from ethyl (5*RS*,3''*SR*)-1-[2'-(4''-ethoxycarbonylphenoxy)-ethyl]-2-oxo-5-[3''' - (2'''' - tetrahydropyranyloxy)-*trans*-1'''-octenyl]-cyclopentane-carboxylate.

Rf = 0.35 (cyclohexane/ethyl acetate/glacial ac tic acid 40:60:1)

NMR: 7.45 ppm (4H, quadruplet), 6.3 ppm (2H), 5.65 ppm (2H), 4.15 ppm (3H).

EXAMPLE 15.

rac. 1,7-*inter*-(2,5-furylidene)-15α-hydroxy-9-oxo-2,3,4,5,6-pentanor-13-trans-prostenoic acid

The above compound was prepared by a process analogous to that described in Example 3, starting from ethyl (5*RS*,3''*SR*)-1-(5'-ethoxycarbonylfurfuryl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.

Rf = 0.13 (silica gel, cyclohexane/ethyl acetate/glacial acetic acid 30:70:1)

NMR in $CDCl_3$: 7.1—7.3 ppm (1H, dublet)
6.5 ppm (2H, singulet)
6.2 ppm (1H, dublet)
5.5—5.7 ppm (2H, multiplet)
4—4.1 ppm (1H, multiplet).

EXAMPLE 16.

rac. 9ξ,15α-Dihydroxy-3-oxa-5-*trans*, 13-trans-prostadienoic acids (A and B)

140 mg of rac. 15α-hydroxy-3-oxa-9-oxo-5-*trans*, 13-*trans*-prostadienoic acid were dissolved in 20 ml of methanol and during the course of 1.5 hours 3 x 150 mg of sodium borohydride were added. The reaction solution was adjusted to pH 7 with glacial acetic acid, the solvent was distilled off under reduced pressure. The residue was acidified in 10 ml of H_2O with 2 N HCl to pH 1 and was extracted three times with 100 ml portions of ether. The combined ether extracts were washed with water, dried over sodium sulfate and the solvent was distilled off under reduced pressure.

The reaction product (140 mg) was a mixture of two epimers with respect to the position of the hydroxy groups in 9-position. The epimer (fraction A) which runs more rapidly over silica gel, was purified was chromatography on 4 g of silica gel (Merck).

Using 200 ml of cyclohexane/ethyl acetate, 1:9 there were eluted:

A) 30 mg Rf = 0.45 (silica gel, ethyl acetate/methanol 70:35) and using 200 ml of ethyl acetate/methanol 8:2

B) 44 mg showing two spots in the DC (mixture of both epimers)
Rf = 0.45 (silica gel, ethyl acetate/methanol 70:35)
Rf = 0.39.

NMR of fraction A: 5.5—5.8 ppm (4H, multiplet)
4.7 ppm (3H, singulet)
4—4.2 ppm (6H, singulet and multiplet)

NMR of fraction B: 5.5—5.8 ppm (4H, multiplet)
5.2 ppm (3H, singulet)
4—4.1 ppm (6H, singulet and multiplet)

EXAMPLE 17.

rac. 9ξ,15α-Dihydroxy-1,5-*inter-p*-phenylene-2,3,4-trinor-13-trans-prostenoic acid

Reactions were carried out in a manner analogous to those described in Example 29, starting from rac. 15α-hydroxy-9-oxo-1,5-*inter-p*-phenylene-2,3,4-trinor-13-*trans*-prostenoic acid.

Rf-value of the more faster-moving isomer: 0.23 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1).

NMR-spectrum: 7.6 ppm (4H, A_2B_2-type), 5.5 ppm (2H), 4.4—3.9 ppm (5H).

Slower isomer: m.p. 124 to 126°C.

Rf-value = 0.19 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1).

NMR: 7.6 ppm (4H, A_2B_2-type), 5.45 ppm (2H), 4.3—3.7 ppm (5H).

EXAMPLE 18.

rac. 9ξ,15α-Dihydroxy-3-oxa-5-cis-13-trans-prostadienic acid

In a manner analogous to that described in Example 29 there were obtained from 150 mg of rac. 15α-hydroxy-3-oxa-9-oxo-5-*cis*, 13-*trans*-prostadienoic acid 82 mg of rac. 9ξ,15α-dihydroxy-3-oxa-5-*cis*, 13-*trans*-prostadienic acid.

Rf = 0.43 (silica gel, ethyl acetate/methanol 70:35)
NMR in $CDCl_3$: 5.4—5.7 ppm (4H, multiplet)
5 ppm (3H, singulet)
3.9—4.3 ppm (6H, singulet and multiplet).

EXAMPLE 19.

rac. 19ξ,15α-Dihydroxy-3-oxa-2a-homo-5-*cis*, 13-*trans*-prostadienoic acid

In an analogous manner to that described in Example 29 the above compound was obtained from rac. 15α-hydroxy-3-oxa-9-oxo-2a-homo-5-*cis*, 13-*trans*-prostadienoic acid.

Rf = 0.55 (silica gel, ethyl acetate/methanol 70:35)
NMR in $CDCl_3$: 5.4—5.7 ppm (4H, multiplet)
5.0 ppm (3H, singulet)
3.9—4.3 ppm (6H, multiplet)

EXAMPLE 20.

rac. 15α-Hydroxy-5-methyl-9-oxo-5-*trans*-13-*trans*-prostadienoic acid

The above compound was obtained by a method analogous to that described in Example 3 from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-3'-methyl-*trans*-2'-hexenyl)-2-oxo-5-[3''-(2''' - tetrahydropyranyloxy)-trans-1''-octenyl]-cyclopentanecarboxylate.

NMR in $CDCl_3$: 6.2 ppm (2H), 5.6 ppm (2H), 5.1 ppm (1H), 4.1 ppm (1H).

EXAMPLE 21.

rac. 9ξ,15α-Dihydroxy-5-methyl-13-trans-prostenoic acid

The product was obtained in a manner analogous to that described in Example 30 from rac. 15α-hydroxy-5-methyl-9-oxo-13-*trans*-prostenoic acid.

NMR in $CDCl_3$: 5.5 ppm (5H), 4.2 ppm (2H).

EXAMPLE 22.

rac. 15α-Hydroxy-6-methyl-9-oxo-13-trans-prostenoic acid

The above compound was obtained in a manner analogous to that described in Example 3 from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-2'-methylhexyl)-2-oxo-5-[3'' - (2''' - tetrahydropyranyloxy) - *trans* - 1'' - octenyl] - cyclopentanecarboxylate. Rf-value and NMR-spectrum: practically identical with that described in Example 5.

EXAMPLE 23.

rac. 15α-Hydroxy-4-ethyl-9-oxo-13-trans-prostenoic acid

This compound was obtained in a manner analogous to that of Example 3 from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-4'-ethylhexyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.

Rf = 0.35 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1).

EXAMPLE 24.

rac. 15α-Hydroxy-5-ethyl-9-oxo-13-trans-prostenoic acid

The above compound was obtained in a manner analogous to that described in Example 3 from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-3'-ethylhexyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)--trans-1''-octenyl]-cyclopentanecarboxylate.

NMR in $CDCl_3$: 6.3 ppm (2H), 5.6 ppm (2H), 4.1 ppm (1H).

EXAMPLE 25.

rac. 15α-Hydroxy-6-ethyl-9-oxo-13-trans-prostenoic acid

This compound was obtained in a manner analogous described in Example 3 from ethyl (5*RS*,3''*SR*)-1-(6'-ethoxycarbonyl-2'-ethylhexyl)-2-oxo-5-[3''-(2'''-tetrahydropyranyloxy)-*trans*-1''-octenyl]-cyclopentanecarboxylate.

Rf = 0.32 (cyclohexane/ethyl acetate/glacial acetic acid 40:60:1).

EXAMPLE 26.

rac. 15α-Hydroxy-9-oxo-4-oxa-1,4-*inter-o*-phenylene-2,3-dinor-13-trans-prostenoic acid

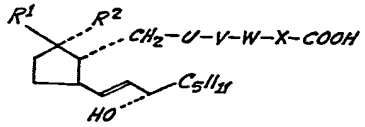
The product was obtained in a manner analogous to that described in Example 3 from ethyl (5*RS*,3''*SR*)-1-[3'-(2''-ethoxycarbonylphenoxy)-propyl]-2-

oxo - 5 - [3''' - (2'''' - tetrahydropyranyloxy) - *trans* - 1''' - octenyl] - cyclopentane-carboxylate.

NMR in $CDCl_3$: 6.8—8.2 ppm (4H, multiplet)
6.4 ppm (2H, singulet)
5.7 ppm (2H)
4.2 ppm (3H).

WHAT WE CLAIM IS:—

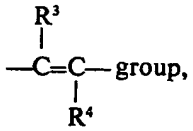
1. A compound of the general formula I



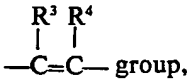
(I)

wherein R^1 and R^2 together represent an oxygen atom or one represents a hydrogen atom and the other represents a hydroxyl group;

U represents a $(CH_2)_m$-group, m being 0 or an integer of from 1 to 5, an

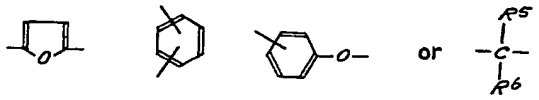


wherein R^3 and R^4, which may be identical or different, each represents a hydrogen atom or an alkyl group having up to 5 carbon atoms, or an



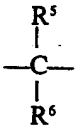
wherein R^3 and R^4 are as defined above;

V represents a direct bond, a oxygen atom or a radical of the formula



wherein R^5 and R^6, which may be identical or different, each represents a hydrogen atom or an alkyl group having up to 5 carbon atoms,

W represents a direct bond or a radical of the formula



wherein R^5 and R^6, which may be identical or different, each represents a hydrogen atom or an alkyl group having up to 5 carbon atoms;

X represents a $(CH_2)_m$-group, wherein m is 0 or an integer of from 1 to 5; subject to the following provisos:

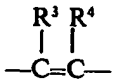
(i) when U represents a $(CH_2)_m$ group, V, W and X together do not represent a straight-chain alkylene group, an alkylene group in which the carbon atoms adjacent to the carboxyl group (position 2) is substituted by one alkyl group, or an alkylene group in which the carbon atom in position 3 is substituted by two alkyl groups,

(ii) when U represents a $(CH_2)_m$ group and V and W both represent direct bonds, X does not represent a $(CH_2)_m$ group in which m is 0,

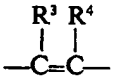
(iii) when U represents a $(CH_2)_m$ group and V represents an oxygen atom, W

and X together do not represent a methylene group, or a trimethylene group which may be substituted by one alkyl group, and

(iv) when U represents the group

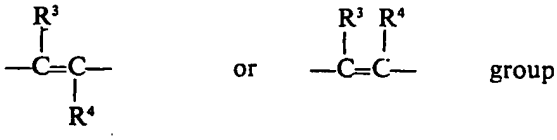


in which R^3 and R^4 both represent hydrogen atoms, V, W and X together do not represent an alkylene group having up to 10 carbon atoms with 1 to 5 carbon atoms in the chain between the carboxyl group and the



group.

2. A compound as claimed in claim 1, wherein U represents a polymethylene chain having up to 3 methylene groups or represents a



wherein R^3 and R^4, which may the same or different, each represents an alkyl group having up to 3 carbon atoms, the radical V, W and X together form a branched alkylene radical having up to 10 carbon atoms, an oxa-branched alkylene radical having up to 9 carbon atoms, or an oxa-straight chain alkylene radical having up to 6 carbon atoms, and R^1 and R^2 are defined as in claim 1.

3. 15α-Hydroxy-3-oxa-9-oxo-5-*trans*, 13-*trans*-prostadienoic acid.

4. 15α-Hydroxy-3-oxa-9-oxo-5-*cis*, 13-*trans*-prostadienoic acid.

5. 15α-Hydroxy-5-methyl-9-oxo-13-*trans*-prostenoic acid.

6. 15α-hydroxy-6-methyl-9-oxo-13-*trans*-prostenoic acid.

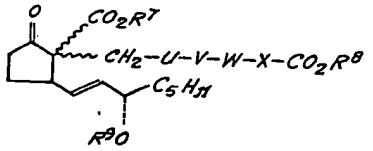
7. A compound as claimed in Claim 1 and which is named in List A or in any one of the Examples herein, with the exception of the compounds claimed in Claims 3 to 6.

8. A salt of a compound as claimed in any one of Claims 1 to 7.

9. A physiologically tolerable salt of a compound as claimed in any one of Claims 1 to 7.

10. A process for the manufacture of a compound as claimed in Claim 1, which comprises

a) reacting an alkali metal alkoxide with a compound of the general formula II



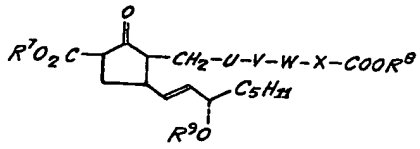
(II)

wherein U, V, W and X are defined as in Claim 1 and

R^7 represents an alkyl group having up to 5 carbon atoms,

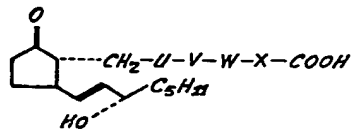
R^8 represents an alkyl group having up to 5 carbon atoms,

R^9 represents an unsubstituted or substituted alkyl group having up to 20 carbon atoms, an aryl radical, or a cycloalkyl radical having from 5 to 8 carbon atoms wherein a CH_2-group may be replaced by an oxygen atom, and subjecting the reaction product of the general formula III



(III)

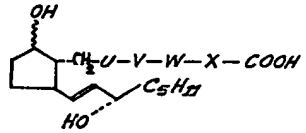
wher in the radicals R^7, R^8 and R^9 and U, V, W and X are defined as in the formula II, to alkaline hydrolysis, decarboxylation and removal of the protective group from the 15-position in the presence of an acid catalyst, whereupon a compound of the general formula Ia



(Ia)

wherein U, V, W and X are defined as in Claim 1, or a salt thereof is obtained; and, if desired,

b) reducing a compound of the general formula Ia with a complex metal hydride to give a compound of the general formula Ib



(Ib)

wherein the 9-hydroxy group may be in the α- or β-configuration and U, V, W and X are defined as in Claim 1; and if desired,

c) converting a resulting salt into the free acids or a resulting salt into the free acid or another salt.

11. A process as claimed in Claim 10, conducted substantially as described in any one of the Examples herein.

12. A compound as claimed in any one of Claims 1 to 9, whenever produced by a process as claimed in Claim 10.

13. A pharmaceutical preparation which comprises a compound as claimed in any one of Claims 1 to 7 or Claim 9 in admixture or conjunction with a pharmaceutically suitable carrier.

14. A pharmaceutical preparation as claimed in Claim 13, in the form of an aqueous suspension or solution.

15. A pharmaceutical preparation as claimed in Claim 13, wherein the carrier is a polymer carrier.

16. A pharmaceutical preparation as claimed in Claim 15, wherein the polymer carrier is polyvinyl pyrrolidone.

17. A pharmaceutical preparation as claimed in Claim 13, in the form of an aerosol.

18. A pharmaceutical preparation as claimed in Claim 13, in a form suitable for administration by injection or infusion.

19. A pharmaceutical preparation as claimed in Claim 13, in a form suitable for oral or rectal administration.

20. A pharmaceutical preparation as claimed in Claim 18 or Claim 19, in unit dosage form.

21. A pharmaceutical preparation as claimed in Claim 20, which comprises from 1 mg to 10 mg of the compound or salt thereof per unit dose.

22. A pharmaceutical preparation as claimed in Claim 13, in a form suitable for topical administration.

23. A pharmaceutical preparation as claimed in any one of Claims 13 to 22, which also comprises one or more other pharmacologically active substances.

24. A pharmaceutical preparation as claimed in Claim 23, wherein the other pharmacologically active substance(s) is or are selected from diretic, hypotensive and antiasthmatic agents.

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